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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,823	12/20/2006	Mladen Mercep	PLP537USw	2037

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EXAMINER	
JARRELL, NOBLE E	
ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
09/08/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/587,823	MERCEP ET AL.	
	Examiner	Art Unit	
	NOBLE JARRELL	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-9 and 13-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-9 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/5/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The rejections under 35 U.S.C. 1st paragraph for solvates and written description have been overcome by the amendment filed 5/5/09.

2. The rejection under 35 U.S.C. 112 2nd paragraph regarding the disorders to be treated has been overcome by the amendment filed 5/5/09.

3. In the amended claim set, claims 1, 2, 3, 5, 6, 7, 8, 9, 13, 14, and 15 are pending are being examined on the merits.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Newly amended claims 1, 2, 3, 5, 6, 7, 8, 9, 13, 14, and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *in vitro* binding of compounds of claim 1 to 5-HT_{2A}, 5-HT_{2C}, and σ1 receptors and testing of compounds of claim 1 in mice and rats, does not reasonably provide enablement for the simultaneous alleviation and prevention (applicants define treatment as prevention and alleviation, page 22, paragraph 2) of any of the disorders listed in claim 1 as well the alleviation or prevention of any of these disorders in humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed

is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method of treating (which includes both alleviation and prevention) disorders, damage, or disease(s) linked to modulation of biogenic amines or neurotransmitters with compounds composed of a dibenzo[*b,f*]thieno[3,2-*d*]oxepine or dibenzo[*b,f*]thieno[3,2-*d*]thiepine ring which is further fused with C_6 ring. Thus, the claims taken together with the specification imply that compounds of the instant invention can treat ailments caused by the equilibrium of biogenic amines or neurotransmitters.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Nitu et al. (*Expert Opinion in Investigational Drugs*, **2003**, *12(4)*, 545-59, cited in previous office action) teach that that topiramate, a glutamate (a neurotransmitter) antagonist, does not show efficacy in phase III clinical trials, and thus cannot work *in vivo* (section 3.3.4). This paper shows that even though a compound may work effectively *in vitro*, that does not necessarily guarantee that the compound will work *in vivo*.

Bhatt et al. (*Expert Opinion in Investigational Drugs*, **2007**, *16(8)*, 1197-1207, cited in previous office action) teach there is no *in vitro* model for glutamate inhibition that ensures clinical success (page 1203, section 5, paragraph 3).

Serretti et al. (*Expert Opinion in Therapeutic Targets*, **2004**, *8(1)*, 15-23, cited in previous office action) teach that 5-HT_{2c} receptors cannot be considered to be a potential target drug target for mood disorders (section 8, page 20).

Wood (*Expert Opinion in Investigational Drugs*, **2002**, *11(4)*, 457-67, cited in previous office action) teaches that inhibition of 5-HT receptors, although it may work *in vitro*, may not work *in vivo* (inhibition is not shown to be efficacious) (page 461, section 3.2).

Ogren (*Nuclear Medicine and Biology*, **1998**, *25*, 747-749) teach that a major hurdle for the relevance of animal models is that 5-HT related effects cannot be measured reliably. Anxiety is cited as one example by Ogren et al. The mouse/rat to human correlation is still not reliable because the role of 5-HT is still unclear (pages 747-749).

Pulley et al. (US 7067507, published 27 June 2006) teach that prevention of Alzheimer's disease (a neurodegenerative disease) is not possible (column 2, lines 40-44).

(5) The relative skill of those in the art:

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this art is MD's, PhD's, or those with advanced degrees and the requisite experience in treatment of a disorder related to the equilibrium of a biogenic amine or other neurotransmitter.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for the *in vitro* binding of compounds of claim 1 to 5-HT_{2A}, 5-HT_{2C}, and σ1 receptors and testing of compounds of claim 1 in mice and rats (specification pages 23-28).

However, the specification does not provide guidance for the simultaneous alleviation and prevention (applicants define treatment as prevention and alleviation) of any of the disorders listed in claim 1 as well the alleviation or prevention of any of these disorders in humans. Simultaneous prevention and alleviation of a disorder is not possible. When a subject has a disorder, only alleviation is possible. When one does not have a disorder yet, prevention is possible.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claims 1, 2, 3, 5, 6, 7, 8, 9, 13, 14, and 15 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Newly amended claims 1, 2, 3, 5, 6, 7, 8, 9, 13, 14, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In terms of the biogenic amines, it is unclear what biogenic amines and neurotransmitters are targeted. The Medical Subject Headings thesaurus (MeSH) ("Biogenic Amines", "Biogenic Monoamines", and "Biogenic Polyamines", http://www.nlm.nih.gov/cgi/mesh/2008/MB_cgi?mode=&term=Biogenic+Amines&field=entry, accessed December 6, 2008; "Neurotransmitter Agents", http://www.nlm.nih.gov/cgi/mesh/2008/MB_cgi, accessed December 6, 2008, both attached as PDF documents, each document was cited previously) lists several types of biogenic amines and neurotransmitters. The insertion of the disorders into claim 1 renders this claim and its dependent claims indefinite because several of these disorders are unclear. What specific sleeping disorder is being alleviated or prevented ("Sleep disorders",

http://www.nlm.nih.gov/cgi/mesh/2008/MB_cgi?mode=&index=12386&field=all&HM=&II=&PA=&form=&input=, accessed 8 December 2008, attached as PDF)? MeSH lists several types of sleeping disorders. What specific sexual type disorder is being alleviated or prevented ("Sexual and Gender Disorders", http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&index=18561&field=all&HM=&II=&PA=&form=&input=, accessed 27 August 2009, attached as PDF)? MeSH lists several types of sexual disorders. What specific psychotic disorder is being alleviated or prevented "Schizophrenia and Psychotic Disorders", http://www.webmd.com/schizophrenia/guide/mental-health-psychotic-disorders, accessed 28 May 2009, attached as PDF)? WebMD lists several types of psychotic disorders. What specific personality disorder is being alleviated or prevented ("Personality Disorders", http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi, accessed 27 August 2009, attached as PDF)? MeSH lists several types of personality disorders. What specific "organic mental disorder" is being alleviated or prevented ("Delirium, Dementia, Amnestic, Cognitive Disorders", http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&term...m,+Dementia,+Amnestic,+Cognitive+Disorders&field=entry, accessed 1 July 2009, attached as PDF)? MeSH lists more than one type of an "organic mental disorder". What specific addiction is being alleviated or prevented "Substance-related disorders", http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi?mode=&index=18559&field=all&HM=&II=&PA=&form=&input=, Accessed 27 August 2009, attached as PDF)? MeSH lists several types of addictions. What specific trauma is being alleviated or prevented ("Wounds and Injuries", http://www.nlm.nih.gov/cgi/mesh/2009/MB_cgi, Accessed 27 August 2009, attached as PDF)? MeSH lists several types of traumas. What specific neurodegenerative disorder is being alleviated or prevented ("Neurodegenerative diseases", http://www.nlm.nih.gov/cgi/mesh/2008/MB_cgi, accessed 8 December 2008)? MeSH lists several types of neurodegenerative disorders. What specific cardiovascular disorder is being alleviated or prevented ("Cardiovascular diseases",

http://www.nlm.nih.gov/cgi/mesh/2008/MB_cgi, accessed 20 February 2008). MeSH lists several types of cardiovascular disorders. What specific gastrointestinal disorder is being alleviated or prevented ("Gastrointestinal Diseases", http://www.nlm.nih.gov/cgi/mesh/2008/MB_cgi?mode=&index=5541&field=all&HM=&II=&PA=&form=&input=, accessed 8 December 2008, attached as PDF)? MeSH lists several types of gastrointestinal disorders. What disorders are considered similar to bulimia? Is hyperphasia considered similar to bulimia?

Conclusion

8. No claims are allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Noble Jarrell/
Examiner, Art Unit 1624

/James O. Wilson/
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